

IN THE CLAIMS

1 (withdrawn): A method for inhibiting bone metastases and metastatic growth in a patient which comprises administering to the patient in need thereof a therapeutically effective amount of an endothelin ET-A receptor antagonist.

2 (withdrawn): The method of Claim 1 wherein the bone metastases are osteoblastic.

3 (withdrawn): The method of Claim 2 wherein the osteoblastic bone metastases result from the spread of a primary cancer selected from breast, prostate, lung, kidney, thyroid, myeloma, lymphoma, sarcoma, osteosarcoma, and ovarian.

4 (withdrawn): The method of Claim 3 wherein the primary cancer is prostate cancer and the patient is male.

5 (withdrawn): The method of Claim 1 which additionally comprises co-administration of an anticancer drug.

6 (withdrawn): The method of Claim 5 wherein the anticancer drug agent is selected from leuprolide, goserelin, bicalutamide, nilutamide, flutamide, vitamin D, vitamin D analogues, estrogen, estrogen analogues, prednisone, hydrocortisone, ketoconazole, cyproterone acetate, and progesterone.

7 (withdrawn): The method of Claim 1 which additionally comprises the administration of radiation therapy.

8 (withdrawn): The method of Claim 1 which additionally comprises the administration of at least one therapeutic agent which impedes net bone loss.

9 (withdrawn): The method of Claim 8 wherein the therapeutic agent is a bisphosphonate.

10 (withdrawn): The method of Claim 1 wherein the endothelin antagonist is an ET_A-selective endothelin antagonist.

11 (withdrawn): A method for the inhibition of bone loss in a patient which comprises administering to the patient in need thereof a therapeutically effective amount of an endothelin ET-A receptor antagonist.

12 (withdrawn): The method of Claim 11 wherein the patient has cancer.

13 (withdrawn): The method of Claim 11 wherein the cancer is prostate cancer and the patient is male.

14 (withdrawn): The method of Claim 11 which additionally comprises the administration of at least one therapeutic agent which impedes net bone loss.

15 (withdrawn): The method of Claim 14 wherein the therapeutic agent is a bisphosphonate.

16 (withdrawn): A method for the reduction of cancer-related pain in a patient which comprises administering to the patient in need thereof a therapeutically effective amount of an endothelin ET-A receptor antagonist.

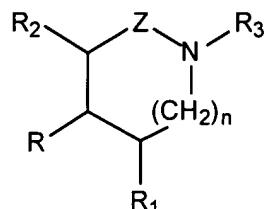
17 (withdrawn): The method of Claim 16 wherein the cancer is prostate cancer and the patient is male.

18 (withdrawn): The method of Claim 16 which additionally comprises the administration of an anticancer drug.

19 (withdrawn): The method of Claim 18 wherein the anticancer drug is selected from leuprolide, goserelin, bicalutamide, nilutamide, flutamide, vitamin D, vitamin D analogues, estrogen, estrogen analogues, prednisone, hydrocortisone, ketoconazole, cyproterone acetate, and progesterone.

20 (withdrawn): The method of Claim 17 which additionally comprises the administration of radiation therapy.

21 (withdrawn): A method for inhibiting bone metastases in a patient which comprises administering to the patient in need thereof a therapeutically effective amount of a compound of formula I:



I

wherein

R is -(CH₂)_m-W;

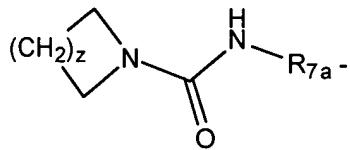
Z is selected from -C(R₁₈)(R₁₉)- and -C(O)-;

R₁ and R₂ are independently selected from hydrogen, loweralkyl, alkenyl, alkynyl, alkoxyalkyl, alkoxycarbonylalkyl, hydroxyalkyl, haloalkyl, haloalkoxyalkyl, alkoxyalkoxyalkyl, thioalkoxyalkoxyalkyl, cycloalkyl, cycloalkylalkyl, aminocarbonylalkyl, alkylaminocarbonylalkyl, dialkylaminocarbonylalkyl, aminocarbonylalkenyl, alkylaminocarbonylalkenyl, dialkylaminocarbonylalkenyl, hydroxyalkenyl, aryl, arylalkyl, aryloxyalkyl, arylalkoxyalkyl, (Nalkanoyl-N-alkyl)aminoalkyl, alkylsulfonylamidoalkyl, heterocyclic, (heterocyclic)alkyl, and (R_{aa})(R_{bb})N-R_{cc}-,

with the proviso that one or both of R₁ and R₂ is other than hydrogen;

R₃ is selected from R₄-C(O)-R₅-, R₄-R_{5a}-, R₄-C(O)-R₅-N(R₆)-, R₆-S(O)2-R₇-R₂₆-S(O)-R₂₇-, R₂₂-O-C(O)-R₂₃-, loweralkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, aryl, arylalkyl, aryloxyalkyl, heterocyclic, (heterocyclic)alkyl, alkoxyalkyl, alkoxyalkoxyalkyl, and R₁₃-C(O)-CH(R₁₄)-;

R₄ and R₆ are independently selected from (R₁₁)(R₁₂)N-, loweralkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, aryl, arylalkyl, heterocyclic, (heterocyclic)alkyl, alkoxyalkyl, hydroxyalkyl, haloalkyl, haloalkenyl, haloalkoxyalkyl, haloalkoxy, alkoxyhaloalkyl, alkylaminoalkyl, dialkylaminoalkyl, alkoxy, and



R₅ is selected from a covalent bond, alkylene, alkenylene, -N(R₂₀)-R₈-, -R_{8a}-N(R₂₀)-R₈-, -O-R₉-, and -R_{9a}-O-R₉;

R₆ is selected from loweralkyl, haloalkyl, alkoxyalkyl, haloalkoxyalkyl, aryl or arylalkyl;

R₇ is a covalent bond, alkylene, alkenylene -N(R₂₁)-R₁₀-, and -R_{10a}-N(R₂₁)-R₁₀;

R₈ is selected from alkylene and alkenylene;

R₉ is alkylene;

R₁₀ is selected from alkylene and alkenylene;

R₁₁ and R₁₂ are independently selected from hydrogen, loweralkyl, haloalkyl, alkoxyalkyl, haloalkoxyalkylalkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, aryl, heterocyclic, arylalkyl, (heterocyclic)alkyl, hydroxyalkyl, alkoxy, aminoalkyl, trialkylaminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, and carboxyalkyl;

R₁₃ is selected from amino, alkylamino and dialkylamino;

R₁₄ is selected from aryl and R₁₅-C(O)-;

R₁₅ is selected from amino, alkylamino and dialkylamino;

R₁₆ is selected from loweralkyl, haloalkyl, aryl and dialkylamino;

R₁₇ is loweralkyl;

R₁₈ and R₁₉ are independently selected from hydrogen and loweralkyl;

R₂₀ is selected from hydrogen, loweralkyl, alkenyl, haloalkyl, alkoxyalkyl, haloalkoxyalkyl, cylcoalkyl and cycloalkylalkyl;

R₂₁ is selected from hydrogen, loweralkyl, alkenyl, haloalkyl, alkoxyalkyl, haloalkoxyalkyl, aryl and arylalkyl;

R₂₂ is selected from a carboxy protecting group and heterocyclic;

R₂₃ is selected from covalent bond, alkylene, alkenylene and -N(R₂₄)-R₂₅-;

R₂₄ is selected from hydrogen and loweralkyl;

R₂₅ is alkylene;

R₂₆ is selected from loweralkyl, haloalkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, aryl, arylalkyl, heterocyclic, (heterocyclic)alkyl, alkoxyalkyl and alkoxy substituted haloalkyl;

R₂₇ is selected from alkylene and alkenylene;

R_{5a} is selected from alkylene and alkenylene;

R_{7a} is alkylene;

R_{8a} is selected from alkylene and alkenylene;

R_{9a} is alkylene;

R_{10a} is selected from alkylene and alkenylene;

R_{aa} is selected from aryl and arylalkyl;

R_{bb} is selected from hydrogen and alkanoyl;

R_{cc} is alkylene;

m is 0-6;

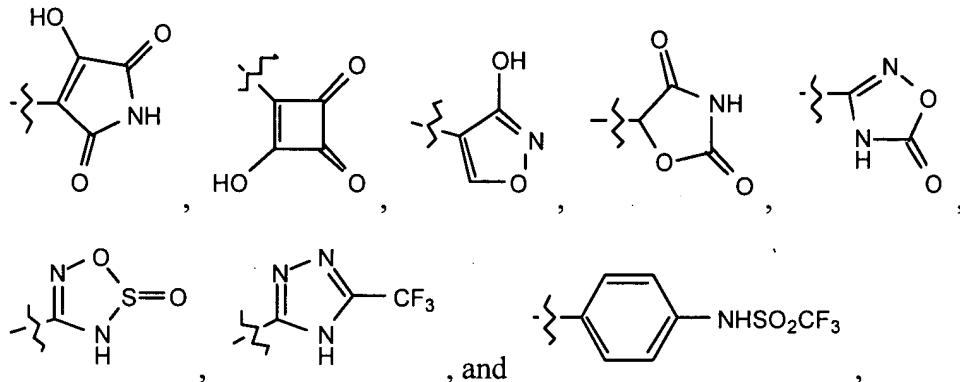
n is 0 or 1;

z is 0-5;

E is selected from hydrogen, loweralkyl and arylalkyl;

G is selected from hydrogen and a carboxy protecting group; and

W is selected from -C(O)2-G; -PO₃H₂, -P(O)(OH)(E), -CN, -C(O)NHR₁₇, alkylaminocarbonyl, dialkylaminocarbonyl, tetrazolyl, hydroxy, alkoxy, sulfonamido, -C(O)NHS(O)2R₁₆, -S(O)2NHC(O)R₁₆,



or a pharmaceutically acceptable salt thereof.

22 (withdrawn): The method of Claim 21 wherein the bone metastases are osteoblastic.

23 (withdrawn): The method of Claim 22 wherein the osteoblastic bone metastases result from the spread of a primary cancer selected from breast, prostate, lung, kidney, thyroid, myeloma, lymphoma, sarcoma, osteosarcoma, and ovarian.

24 (withdrawn): The method of Claim 23 wherein the primary cancer is prostate cancer and the patient is male.

25 (withdrawn): The method of Claim 21 which additionally comprises the administration of an anticancer drug.

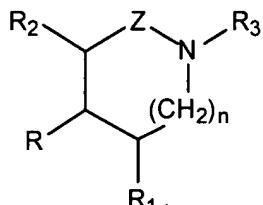
26 (withdrawn): The method of Claim 25 wherein the additional anticancer drug is selected from leuprolide, goserelin, bicalutamide, nilutamide, flutamide, vitamin D, vitamin D analogues, estrogen, estrogen analogues, prednisone, hydrocortisone, ketoconazole, cyproterone acetate, and progesterone.

27 (withdrawn): The method of Claim 21 which additionally comprises the administration of radiation therapy.

28 (withdrawn): The method of Claim 21 which additionally comprises the administration of at least one therapeutic agent which impedes net bone loss.

29 (withdrawn): The method of Claim 28 wherein the therapeutic agent is a bisphosphonate.

30 (withdrawn): A method for the inhibition of bone loss in cancer patients which comprises administering to the patient in need thereof a therapeutically effective amount of a compound of formula I:



I

wherein

R is $-(CH_2)_m-W$;

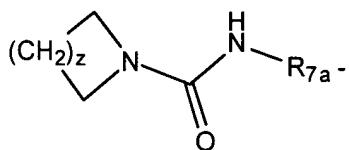
Z is selected from $-C(R_{18})(R_{19})-$ and $-C(O)-$;

R₁ and R₂ are independently selected from hydrogen, loweralkyl, alkenyl, alkynyl, alkoxyalkyl, alkoxy carbonylalkyl, hydroxyalkyl, haloalkyl, haloalkoxyalkyl, alkoxyalkoxyalkyl, thioalkoxyalkoxyalkyl, cycloalkyl, cycloalkylalkyl, aminocarbonylalkyl, alkylaminocarbonylalkyl, dialkylaminocarbonylalkyl, aminocarbonylalkenyl, alkylaminocarbonylalkenyl, dialkylaminocarbonylalkenyl, hydroxyalkenyl, aryl, arylalkyl, aryloxyalkyl, arylalkoxyalkyl, (Nalkanoyl-N-alkyl)aminoalkyl, alkylsulfonylamidoalkyl, heterocyclic, (heterocyclic)alkyl, and $(R_{aa})(R_{bb})N-R_{cc}^-$,

with the proviso that one or both of R₁ and R₂ is other than hydrogen;

R₃ is selected from R₄-C(O)-R₅-, R₄-R_{5a}-, R₄-C(O)-R₅-N(R₆)-, R₆-S(O)2-R₇-R₂₆-S(O)-R₂₇-, R₂₂-O-C(O)-R₂₃-, loweralkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, aryl, arylalkyl, aryloxyalkyl, heterocyclic, (heterocyclic)alkyl, alkoxyalkyl, alkoxyalkoxyalkyl, and R₁₃-C(O)-CH(R₁₄)-;

R₄ and R₆ are independently selected from (R₁₁)(R₁₂)N-, loweralkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, aryl, arylalkyl, heterocyclic, (heterocyclic)alkyl, alkoxyalkyl, hydroxyalkyl, haloalkyl, haloalkenyl, haloalkoxyalkyl, haloalkoxy, alkoxyhaloalkyl, alkylaminoalkyl, dialkylaminoalkyl, alkoxy, and



R₅ is selected from a covalent bond, alkylene, alkenylene, -N(R₂₀)-R₈-, -R_{8a}-N(R₂₀)-R₈-, -O-R₉-, and -R_{9a}-O-R₉-;

R₆ is selected from loweralkyl, haloalkyl, alkoxyalkyl, haloalkoxyalkyl, aryl or arylalkyl;

R₇ is a covalent bond, alkylene, alkenylene -N(R₂₁)-R₁₀-, and -R_{10a}-N(R₂₁)-R₁₀;

R₈ is selected from alkylene and alkenylene;

R₉ is alkylene;

R₁₀ is selected from alkylene and alkenylene;

R₁₁ and R₁₂ are independently selected from hydrogen, loweralkyl, haloalkyl, alkoxyalkyl, haloalkoxyalkylalkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, aryl, heterocyclic, arylalkyl, (heterocyclic)alkyl, hydroxyalkyl, alkoxy, aminoalkyl, trialkylaminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, and carboxyalkyl;

R₁₃ is selected from amino, alkylamino and dialkylamino;

R₁₄ is selected from aryl and R₁₅-C(O)-;

R₁₅ is selected from amino, alkylamino and dialkylamino;

R₁₆ is selected from loweralkyl, haloalkyl, aryl and dialkylamino;

R₁₇ is loweralkyl;

R₁₈ and R₁₉ are independently selected from hydrogen and loweralkyl;

R₂₀ is selected from hydrogen, loweralkyl, alkenyl, haloalkyl, alkoxyalkyl, haloalkoxyalkyl, cylcoalkyl and cycloalkylalkyl;

R₂₁ is selected from hydrogen, loweralkyl, alkenyl, haloalkyl, alkoxyalkyl, haloalkoxyalkyl, aryl and arylalkyl;

R₂₂ is selected from a carboxy protecting group and heterocyclic;

R₂₃ is selected from covalent bond, alkylene, alkenylene and -N(R₂₄)-R₂₅-;

R₂₄ is selected from hydrogen and loweralkyl;

R₂₅ is alkylene;

R₂₆ is selected from loweralkyl, haloalkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, aryl, arylalkyl, heterocyclic, (heterocyclic)alkyl, alkoxyalkyl and alkoxy substituted haloalkyl;

R₂₇ is selected from alkylene and alkenylene;

R_{5a} is selected from alkylene and alkenylene;

R_{7a} is alkylene;

R_{8a} is selected from alkylene and alkenylene;

R_{9a} is alkylene;

R_{10a} is selected from alkylene and alkenylene;

R_{aa} is selected from aryl and arylalkyl;

R_{bb} is selected from hydrogen and alkanoyl;

R_{cc} is alkylene;

m is 0-6;

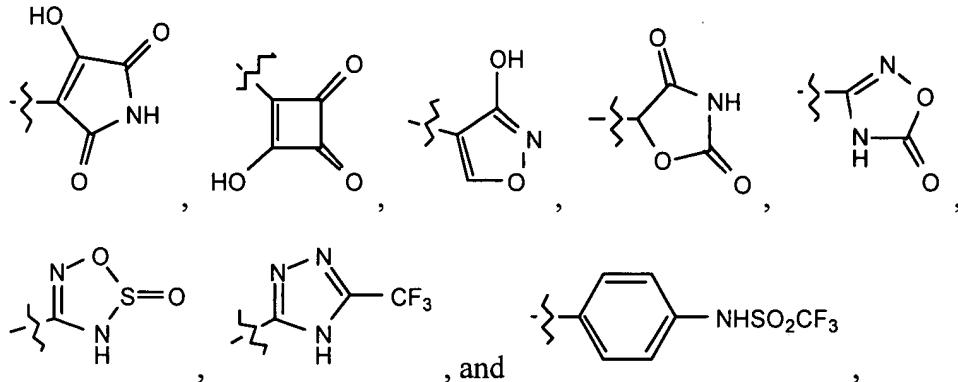
n is 0 or 1;

z is 0-5;

E is selected from hydrogen, loweralkyl and arylalkyl;

G is selected from hydrogen and a carboxy protecting group; and

W is selected from -C(O)2-G; -PO₃H₂, -P(O)(OH)(E), -CN, -C(O)NHR₁₇, alkylaminocarbonyl, dialkylaminocarbonyl, tetrazolyl, hydroxy, alkoxy, sulfonamido, -C(O)NHS(O)₂R₁₆, -S(O)₂NHC(O)R₁₆,



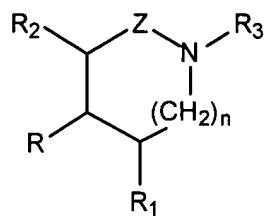
or a pharmaceutically acceptable salt thereof.

31 (withdrawn): The method of Claim 30 wherein the cancer is prostate cancer and the patient is male.

32 (withdrawn): The method of Claim 30 which additionally comprises the administration of at least one therapeutic agent which impedes net bone loss.

33 (withdrawn): The method of Claim 32 wherein the therapeutic agent is a bisphosphonate.

34 (withdrawn): A method for the reduction of cancer-related pain which comprises administering to a patient in need thereof a therapeutically effective amount of a compound of formula I:



I

wherein

R is $-(CH_2)_m-W$;

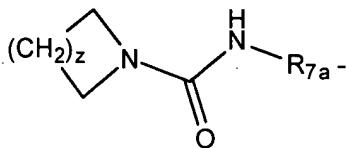
Z is selected from $-C(R_{18})(R_{19})-$ and $-C(O)-$;

R₁ and R₂ are independently selected from hydrogen, loweralkyl, alkenyl, alkynyl, alkoxyalkyl, alkoxycarbonylalkyl, hydroxyalkyl, haloalkyl, haloalkoxyalkyl, alkoxyalkoxyalkyl, thioalkoxyalkoxyalkyl, cycloalkyl, cycloalkylalkyl, aminocarbonylalkyl, alkylaminocarbonylalkyl, dialkylaminocarbonylalkyl, aminocarbonylalkenyl, alkylaminocarbonylalkenyl, dialkylaminocarbonylalkenyl, hydroxyalkenyl, aryl, arylalkyl, aryloxyalkyl, arylalkoxyalkyl, (Nalkanoyl-N-alkyl)aminoalkyl, alkylsulfonylamidoalkyl, heterocyclic, (heterocyclic)alkyl, and $(R_{aa})(R_{bb})N-R_{cc}-$,

with the proviso that one or both of R₁ and R₂ is other than hydrogen;

R₃ is selected from R₄-C(O)-R₅-, R₄-R_{5a}-, R₄-C(O)-R₅-N(R₆)-, R₆-S(O)2-R₇-R₂₆-S(O)-R₂₇-, R₂₂-O-C(O)-R₂₃-, loweralkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, aryl, arylalkyl, aryloxyalkyl, heterocyclic, (heterocyclic)alkyl, alkoxyalkyl, alkoxyalkoxyalkyl, and R₁₃-C(O)-CH(R₁₄)-;

R₄ and R₆ are independently selected from (R₁₁)(R₁₂)N-, loweralkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, aryl, arylalkyl, heterocyclic, (heterocyclic)alkyl, alkoxyalkyl, hydroxyalkyl, haloalkyl, haloalkenyl, haloalkoxyalkyl, haloalkoxy, alkoxyhaloalkyl, alkylaminoalkyl, dialkylaminoalkyl, alkoxy, and



R₅ is selected from a covalent bond, alkylene, alkenylene, -N(R₂₀)-R₈-, -R_{8a}-N(R₂₀)-R₈-, -O-R₉-, and -R_{9a}-O-R₉-;

R₆ is selected from loweralkyl, haloalkyl, alkoxyalkyl, haloalkoxyalkyl, aryl or arylalkyl;

R₇ is a covalent bond, alkylene, alkenylene -N(R₂₁)-R₁₀-, and -R_{10a}-N(R₂₁)-R₁₀;

R₈ is selected from alkylene and alkenylene;

R₉ is alkylene;

R₁₀ is selected from alkylene and alkenylene;

R₁₁ and R₁₂ are independently selected from hydrogen, loweralkyl, haloalkyl, alkoxyalkyl, haloalkoxyalkylalkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, aryl, heterocyclic, arylalkyl, (heterocyclic)alkyl, hydroxyalkyl, alkoxy, aminoalkyl, trialkylaminoalkyl, alkylaminoalkyl, dialkylaminoalkyl, and carboxyalkyl;

R₁₃ is selected from amino, alkylamino and dialkylamino;

R₁₄ is selected from aryl and R₁₅-C(O)-;

R₁₅ is selected from amino, alkylamino and dialkylamino;

R₁₆ is selected from loweralkyl, haloalkyl, aryl and dialkylamino;

R₁₇ is loweralkyl;

R₁₈ and R₁₉ are independently selected from hydrogen and loweralkyl;

R₂₀ is selected from hydrogen, loweralkyl, alkenyl, haloalkyl, alkoxyalkyl, haloalkoxyalkyl, cycloalkyl and cycloalkylalkyl;

R₂₁ is selected from hydrogen, loweralkyl, alkenyl, haloalkyl, alkoxyalkyl, haloalkoxyalkyl, aryl and arylalkyl;

R₂₂ is selected from a carboxy protecting group and heterocyclic;

R₂₃ is selected from covalent bond, alkylene, alkenylene and -N(R₂₄)-R₂₅-;

R₂₄ is selected from hydrogen and loweralkyl;

R₂₅ is alkylene;

R₂₆ is selected from loweralkyl, haloalkyl, alkenyl, alkynyl, cycloalkyl, cycloalkylalkyl, aryl, arylalkyl, heterocyclic, (heterocyclic)alkyl, alkoxyalkyl and alkoxy-substituted haloalkyl;

R₂₇ is selected from alkylene and alkenylene;

R_{5a} is selected from alkylene and alkenylene;

R_{7a} is alkylene;

R_{8a} is selected from alkylene and alkenylene;

R9a is alkylene;

R_{10a} is selected from alkylene and alkenylene;

R_{aa} is selected from aryl and arylalkyl;

R_{bb} is selected from hydrogen and alkanoyl;

R_{CC} is alkylene;

m is 0-6;

n is 0 or 1;

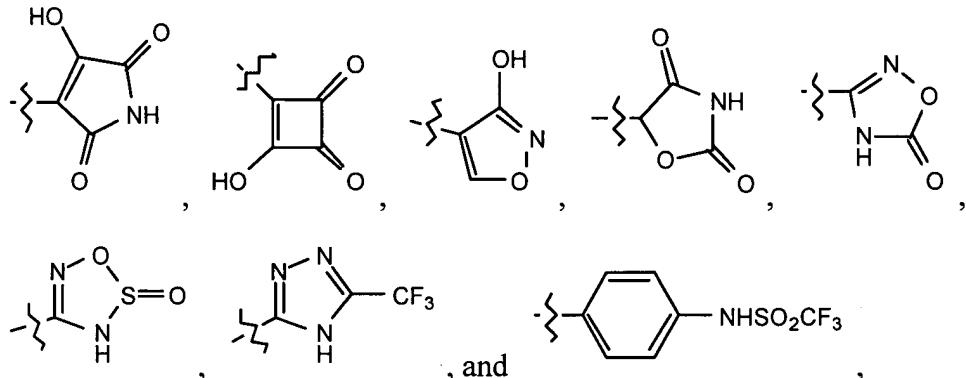
z is 0-5;

E is selected from hydrogen, loweralkyl and arylalkyl;

G is selected from hydrogen and a carboxy protecting group; and

W is selected from $-C(O)2-G$; $-PO_3H_2$, $-P(O)(OH)(E)$,

-CN, -C(O)NHR₁₇, alkylaminocarbonyl, dialkylaminocarbonyl, tetrazolyl, hydroxy, alkoxy, sulfonamido, -C(O)NHS(O)₂R₁₆, -S(O)₂NHC(O)R₁₆,



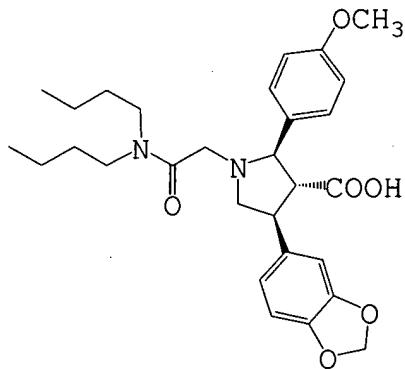
or a pharmaceutically acceptable salt thereof.

35 (withdrawn): The method of Claim 34 wherein the cancer is prostate cancer and the patient is male.

36 (withdrawn): The method of Claim 34 which additionally comprises the administration of an anticancer drug.

37 (withdrawn): The method of Claim 36 wherein the additional anticancer drug is selected from leuprolide, goserelin, bicalutamide, nilutamide, flutamide, vitamin D, vitamin D analogues, estrogen, estrogen analogues, prednisone, hydrocortisone, ketoconazole, cyproterone acetate, and progesterone.

38 (currently amended): A method for inhibiting bone metastases from prostate cancer in a patient having prostate cancer which comprises human comprising administering thereto to the patient a therapeutically effective amount of a compound of formula III



III,

or a pharmaceutically acceptable salt thereof.

39 (original): The method of Claim 38 wherein the bone metastases are osteoblastic.

40 (withdrawn): The method of Claim 39 wherein the osteoblastic bone metastases result from the spread of a primary cancer selected from breast, prostate, lung, kidney, thyroid, myeloma, lymphoma, sarcoma, osteosarcoma, and ovarian.

41 (withdrawn): The method of Claim 40 wherein the primary cancer is prostate cancer and the patient is male.

42 (currently amended): The method of Claim 40 38 which additionally comprises administering an anticancer drug.

43 (original): The method of Claim 42 wherein the anticancer drug is selected from the group consisting of leuprolide, goserelin, bicalutamide, nilutamide, flutamide, vitamin D, vitamin D analogues, estrogen, estrogen analogues, prednisone, hydrocortisone, ketoconazole, cyproterone acetate, and progesterone.

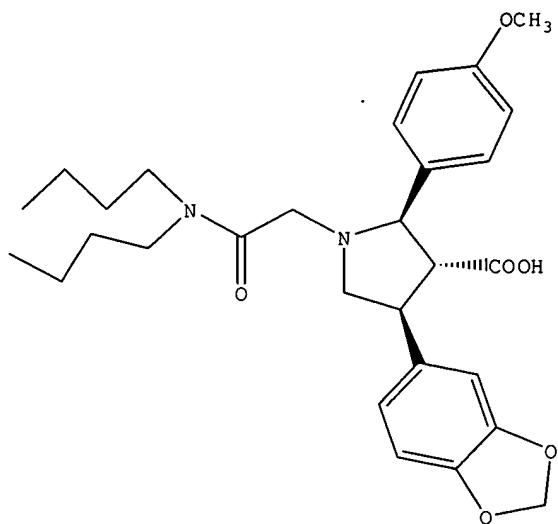
44 (currently amended): The method of Claim 40 38 which additionally comprises administering radiation.

45 (currently amended): The method of Claim 40 38 which additionally comprises administering at least one therapeutic agent which impedes net bone loss.

46 (original): The method of Claim 45 wherein the therapeutic agent is a bisphosphonate.

47 (withdrawn): The method of Claim 40 wherein the endothelin antagonist is an ET_A-selective endothelin antagonist.

48 (withdrawn): A method for the inhibition of bone loss in cancer patients which comprises administering to the patient in need thereof a therapeutically effective amount of a compound of formula III



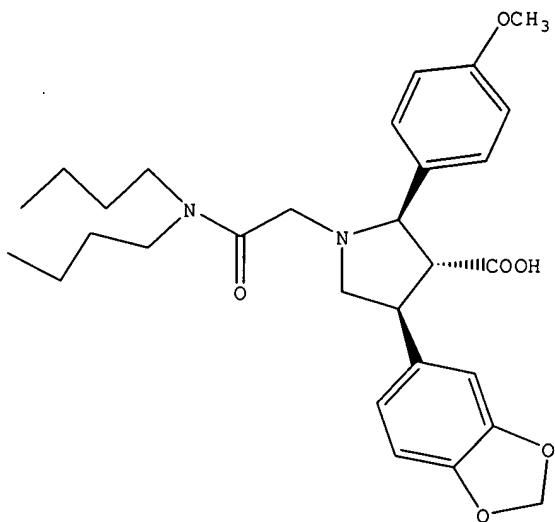
III.

49 (withdrawn): The method of Claim 48 wherein the cancer is prostate cancer and the patient is male.

50 (withdrawn): The method of Claim 48 which additionally comprises the administration of at least one therapeutic agent which impedes net bone loss.

51 (withdrawn): The method of Claim 50 wherein therapeutic agent is a bisphosphonate.

52 (withdrawn): A method for the reduction of cancer-related pain which comprises administering to a patient in need thereof a therapeutically effective amount of a compound of formula III



III.

53 (withdrawn): The method of Claim 52 wherein the cancer is prostate cancer and the patient is male.

54 (withdrawn): The method of Claim 52 which additionally comprises the administration of an anticancer drug.

55 (withdrawn): The method of Claim 54 wherein the anticancer drug is selected from leuprolide, goserelin, bicalutamide, nilutamide, flutamide, vitamin D, vitamin D analogues, estrogen, estrogen analogues, prednisone, hydrocortisone, ketoconazole, cyproterone acetate, and progesterone.

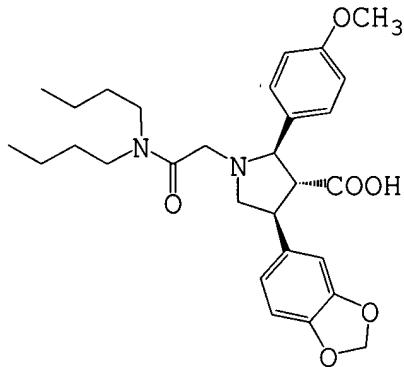
56 (cancelled)

57 (withdrawn): A method for inhibiting metastatic growth in a patient which comprises administering to the patient in need thereof a therapeutically effective amount of an endothelin ET-A receptor antagonist.

58 (withdrawn): A method for inhibiting bone turnover in a patient which comprises administering to the patient in need thereof a therapeutically effective amount of an endothelin ET-A receptor antagonist.

59-64 (canceled)

65 (amended): A method for inhibiting metastatic growth from prostate cancer in a patient having prostate cancer which comprises administering thereto to the patient a therapeutically effective amount of a compound of formula III



III,

or a pharmaceutically acceptable salt thereof.

66 (original): The method of Claim 65 wherein the bone metastases are metastatic growth is osteoblastic metastatic growth.

67 (original): The method of Claim 65 which additionally comprises administering an anticancer drug.

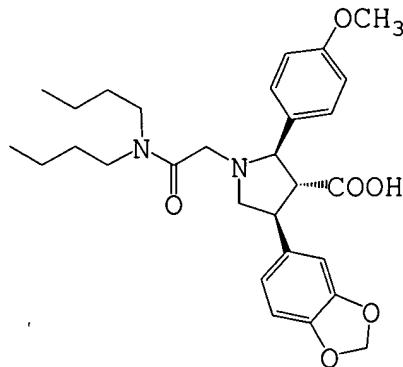
68 (original): The method of Claim 67 wherein the anticancer drug is selected from the group consisting of leuprolide, goserelin, bicalutamide, nilutamide, flutamide, vitamin D, vitamin D analogues, estrogen, estrogen analogues, prednisone, hydrocortisone, ketoconazole, cyproterone acetate, and progesterone.

69 (original): The method of Claim 65 which additionally comprises administering radiation.

70 (original): The method of Claim 65 which additionally comprises administering at least one therapeutic agent which impedes net bone loss.

71 (original): The method of Claim 70 wherein the therapeutic agent is a bisphosphonate.

72 (new): A method for inhibiting osteoblastic bone metastases from prostate cancer in a human comprising administering thereto a therapeutically effective amount of a compound of formula III



III,

or a pharmaceutically acceptable salt thereof.

73 (new): The method of Claim 72 which additionally comprises administering an anticancer drug.

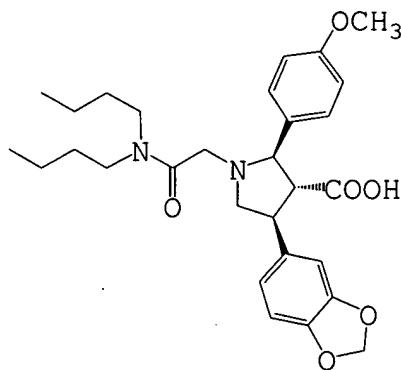
74 (new): The method of Claim 73 wherein the anticancer drug is selected from the group consisting of leuprolide, goserelin, bicalutamide, nilutamide, flutamide, vitamin D, vitamin D analogues, estrogen, estrogen analogues, prednisone, hydrocortisone, ketoconazole, cyproterone acetate, and progesterone.

75 (new): The method of Claim 72 which additionally comprises administering radiation.

76 (new): The method of Claim 72 which additionally comprises administering at least one therapeutic agent which impedes net bone loss.

77 (original): The method of Claim 76 wherein the therapeutic agent is a bisphosphonate.

78 (new): A method for inhibiting osteoblastic metastatic growth from prostate cancer in a human comprising administering thereto a therapeutically effective amount of a compound of formula III



III,

or a pharmaceutically acceptable salt thereof.

79 (new): The method of Claim 78 which additionally comprises administering an anticancer drug.

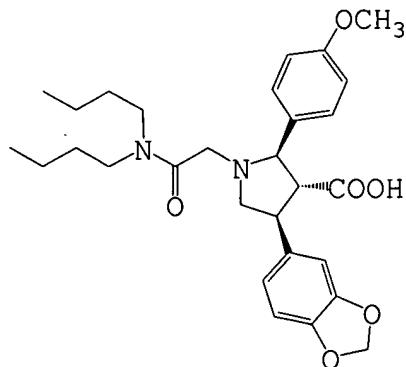
80 (new): The method of Claim 79 wherein the anticancer drug is selected from the group consisting of leuprolide, goserelin, bicalutamide, nilutamide, flutamide, vitamin D, vitamin D analogues, estrogen, estrogen analogues, prednisone, hydrocortisone, ketoconazole, cyproterone acetate, and progesterone.

81 (new): The method of Claim 78 which additionally comprises administering radiation.

82 (new): The method of Claim 78 which additionally comprises administering at least one therapeutic agent which impedes net bone loss.

83 (original): The method of Claim 82 wherein the therapeutic agent is a bisphosphonate.

84 (new): A method for inhibiting bone metastases from prostate cancer in a human comprising administering thereto a therapeutically effective amount of the hydrochloride salt of a compound of formula III



III.

85 (new): The method of Claim 84 wherein the bone metastases are osteoblastic.

86 (new): The method of Claim 84 which additionally comprises administering an

anticancer drug.

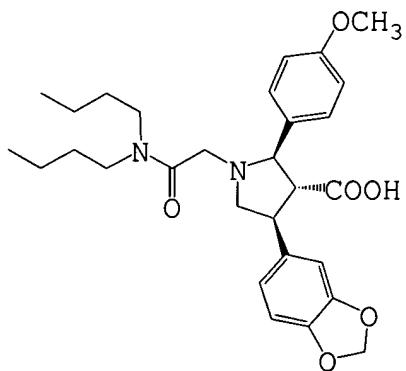
87 (new): The method of Claim 86 wherein the anticancer drug is selected from the group consisting of leuprolide, goserelin, bicalutamide, nilutamide, flutamide, vitamin D, vitamin D analogues, estrogen, estrogen analogues, prednisone, hydrocortisone, ketoconazole, cyproterone acetate, and progesterone.

88 (new): The method of Claim 84 which additionally comprises administering radiation.

89 (new): The method of Claim 84 which additionally comprises administering at least one therapeutic agent which impedes net bone loss.

90 (new): The method of Claim 89 wherein the therapeutic agent is a bisphosphonate.

91 (new): A method for inhibiting metastatic growth from prostate cancer in a human comprising administering thereto a therapeutically effective amount of the hydrochloride salt of a compound of formula III



III.

92 (new): The method of Claim 91 wherein the metastatic growth is osteoblastic metastatic growth.

93 (new): The method of Claim 91 which additionally comprises administering an anticancer drug.

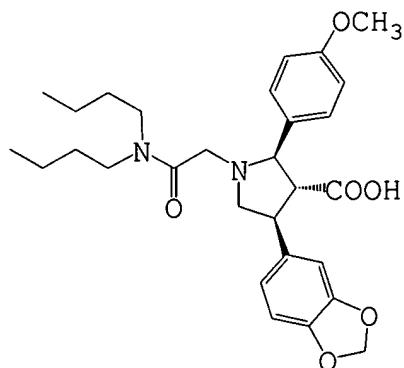
94 (new): The method of Claim 93 wherein the anticancer drug is selected from the group consisting of leuprolide, goserelin, bicalutamide, nilutamide, flutamide, vitamin D, vitamin D analogues, estrogen, estrogen analogues, prednisone, hydrocortisone, ketoconazole, cyproterone acetate, and progesterone.

95 (new): The method of Claim 91 which additionally comprises administering radiation.

96 (new): The method of Claim 91 which additionally comprises administering at least one therapeutic agent which impedes net bone loss.

97 (new): The method of Claim 96 wherein the therapeutic agent is a bisphosphonate.

98 (new): A method for inhibiting osteoblastic bone metastases from prostate cancer in a human comprising administering thereto a therapeutically effective amount of the hydrochloride salt of a compound of formula III



III.

99 (new): The method of Claim 98 which additionally comprises administering an anticancer drug.

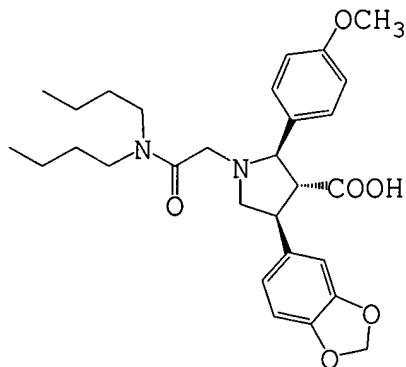
100 (new): The method of Claim 99 wherein the anticancer drug is selected from the group consisting of leuprolide, goserelin, bicalutamide, nilutamide, flutamide, vitamin D, vitamin D analogues, estrogen, estrogen analogues, prednisone, hydrocortisone, ketoconazole, cyproterone acetate, and progesterone.

101 (new): The method of Claim 98 which additionally comprises administering radiation.

102 (new): The method of Claim 98 which additionally comprises administering at least one therapeutic agent which impedes net bone loss.

103 (new): The method of Claim 102 wherein the therapeutic agent is a bisphosphonate.

104 (new): A method for inhibiting osteoblastic metastatic growth from prostate cancer in a human comprising administering thereto a therapeutically effective amount of the hydrochloride salt of a compound of formula III



III.

105 (new): The method of Claim 104 which additionally comprises administering

an anticancer drug.

106 (new): The method of Claim 105 wherein the anticancer drug is selected from the group consisting of leuprolide, goserelin, bicalutamide, nilutamide, flutamide, vitamin D, vitamin D analogues, estrogen, estrogen analogues, prednisone, hydrocortisone, ketoconazole, cyproterone acetate, and progesterone.

107 (new): The method of Claim 104 which additionally comprises administering radiation.

108 (new): The method of Claim 104 which additionally comprises administering at least one therapeutic agent which impedes net bone loss.

109 (new): The method of Claim 108 wherein the therapeutic agent is a bisphosphonate.

Respectfully submitted,
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